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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/538,245	06/07/2005	David Feifel	034123-122	3580

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EXAMINER	
DUTT, ADITI	
ART UNIT	**PAPER NUMBER**
1649	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/28/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/538,245	FEIFEL, DAVID	
	Examiner	Art Unit	
	Aditi Dutt	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 15-34* is/are pending in the application.

4a) Of the above claim(s) *1-10,19 and 27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-18,20-26,28-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-10,15-34* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 June 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/7/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

1. The amendment of 20 November 2006 has been entered in full.

Election/Restrictions

2 Applicant's election of Group IV without traverse, represented by claims 15-34 drawn to a method for modulating sensorimotor gating or inhibiting serotonin-2A and/or alpha-1 receptor mediated neural function and improving cognitive function by administration of neurotensin agonist to a subject, in the reply filed on 20 November 2006 is acknowledged.

3. Applicant's election of bipolar disorders as species of neuropsychiatric disorder, will be considered for examination. Additionally, during a telephone conversation with Joseph Baker on 13 December 2006, a provisional election was made without traverse, to prosecute the species of NT agonist as NT69L. Affirmation of this election must be made by applicant in replying to this Office action. Claims 19 and 27 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected species.

4. Claims 1-10, 19 and 27, are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 20 November 2006.

5. Claims 15-18, 20-26, 28-34, drawn to a method for modulating sensorimotor gating or inhibiting serotonin-2A and/or alpha-1 receptor mediated neural function and improving cognitive function by administration of neurotensin agonist to a subject, are being considered for examination in the instant application.

Drawings

6. The drawings are objected to because:

"X" and/or "Y" axis should be labeled in Figures 2, 7 and 10.

7. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner,

the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Objections

8. Claims 15-17, 19, 23, 25, 30 and 31 are objected to because of the following informalities:

Claims 15-17, 19, 23, 25, 30 and 31, recite non-elected species.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 15-18, 20-26 and 28-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. The term "modulating" in claim 15-18, 20-23 is a relative term which renders the claim indefinite. The term "modulating" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear what the term “modulating” encompasses. Is it “enhance”, “mimic” or “inhibit”?

11. Claims 24-26 and 28-30 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: an additional step indicating the inhibition of serotonin-2A and/or alpha-1 receptor mediated neural function.

12. The term "improving symptoms in a subject" in claims 16-18, 20 is a relative term which renders the claim indefinite. Firstly, the term "improving" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Further, the claim does neither identify the "subject" nor the "symptoms" encompassed in the claim.

Claim Rejections - 35 USC § 112-Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 15-16, 21-23, 29-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for administration of a neurotensin agonist to a subject with reduced pre-pulse inhibition (PPI), thereby promoting an elevation in the PPI response, does not reasonably provide enablement for a method of modulating sensorimotor gating in a subject having a neuropsychiatric disorder, such as bipolar disorder, by

administering any neurotensin agonist, thereby increasing PPI. Furthermore, the specification does not provide enablement for treating a subject having any neuropsychiatric disorder, and improving cognitive function and memory, by administration of a pharmaceutical dose of any neurotensin agonist. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

14. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, include the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed. The instant disclosure fails to meet the enablement requirement for the following reasons:

15. The claims are drawn to a method for modulating sensorimotor gating in a subject having inherently reduced pre-pulse inhibition (PPI), or any neuropsychiatric disorder, such as bipolar disorder causing a reduced PPI by administering any neurotensin (NT) agonist, to increase PPI (claims 15-16, 21-23). The claims further recite the inhibition of serotonin receptor mediated neural function, or improving cognitive function and memory attention, by administration of a pharmaceutically effective dose of any NT agonist, in a subject having bipolar disorder (claims 29-34). It is noted that the term "modulating" in the claims

is interpreted as "enhance", "mimic" or "inhibit" by the Examiner (see instant specification, page 16, para 0048).

16. With respect to claim breadth, the standard under 35 U.S.C. § 112, first paragraph, entails the determination of what the claims recite and what the claims mean as a whole. In addition, when analyzing the enablement scope of the claims, the teachings of the specification are to be taken into account because the claims are to be given their broadest reasonable interpretation that is consistent with the specification (see MPEP 2111 [R-1]), which states that claims must be given their broadest reasonable interpretation.

17. "During patent examination, the pending claims must be "given *>their< broadest reasonable interpretation consistent with the specification." *In re Hyatt,* 211 F.3d 1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000). Applicant always has the opportunity to amend the claims during prosecution, and broad interpretation by the examiner reduces the possibility that the claim, once issued, will be interpreted more broadly that is justified. *In re Prater,* 415 F.2d 1393, 1404-05, 162 USPQ 541, 550-51 (CCPA 1969)".

18. As such, the broadest reasonable interpretation of the claimed method is for modulating sensorimotor gating comprising administering any neurotensin agonist and treating any neuropsychiatric disease, by improving cognitive function and memory.

19. The specification of the instant application teaches that

sensorimotor gating is a process, whereby the central nervous system regulates and filters incoming environmental information, which is disrupted in neuropsychiatric disorders (pages 1 and 2, para 0005). The specification also teaches that PPI of the acoustic startle reflex, is an operational measure of the sensorimotor gating, that is also reduced in a number of neuropsychiatric illnesses (page 7, para 0027). The specification further teaches that NT is a 13 amino acid neuropeptide, colocalized with dopamine in the brain and periphery, and that NT and NT agonists are implicated to have antipsychotic functions as well as other physiological functions (page 1, para 0004; page 13, para 0039). The specification finally teaches in Example 1, that the NT agonist, NT69L administration in rats reversed the PPI changes induced by serotonin-2A agonist DOI, alpha-1 adrenergic agonist cirazoline (Figures 4-6, 8, 10, page 34-39; page 14, para 0040-0041). However, the specification does not disclose any methods or working examples for modulating sensorimotor gating in a subject having any neuropsychatric disease (e.g. bipolar disorder) causing a reduced PPI, by administering any NT agonist. The specification also does not disclose a method improving cognitive function and memory attention, by administration of a pharmaceutically effective dose of any NT agonist, in a subject having bipolar disorder. Undue experimentation would be required by one skilled in the art, to modulate sensorimotor gating in a subject with any neurodegenerative disorder, by administering any NT agonist.

20. Relevant literature teaches that the NT null mutant mice exhibited significantly increased startle amplitude and significantly reduced PPI than control animals (Kinkead et al., J Pharm Exp Therap 315: 256-264, 2005; page 262, Discussion, para 2). The art further teaches that bipolar disorder patients with acute mania displayed significantly lower PPI than the control group (Perry et al. Biol Psychiatry. 50: 418-424, 2001; Figure 1, page 421). However, the PPI of the acoustic startle response depended on the state of the bipolar disorder in the patient, PPI levels being normal in the euthymic state (Barret et al. Psychol Med 12: 1737-1746, 2005, abstract; page 1742, Figure 1). The art further teaches that serotonin-2A receptor gene is "unlikely to play a major role in the genetic susceptibility to bipolar disorder" and, therefore, in the etiology of bipolar disease (Ni et al. Neuromol Med. 2: 251-9, 2002, abstract, page 256, lines 1-2).

21. Furthermore, the art suggests that because of the "heterogeneous etiologies involving complex interactions among genetic and environmental factors" and because of the involvement of multiple brain functions in the behavioral states in diseases such as schizophrenia, and bipolar disorders, the lack of a valid animal model is a major limitation (Kilts. Biol Psychiatry 50: 845-855, 2001, page 846, column 1, para 1; Einat, J Psycopharmacol 20: 714-722, 2006). As a cautionary note, the art suggests that PPI is only one factor of the disease pathology of various neuropsychiatric illnesses, and "although an induced deficit in PPI in adult rats may have valid relationship to key psychophysiologic impairments related to schizophrenia", and bipolar disorder, "it

might bear no relationship to the pathogenesis of the disorder" (Kilts, page 852, concluding para). Finally, it is well known in the art and further reiterated in the instant specification that "many patients with schizophrenia and other neuropsychiatric illnesses ..... are considered "treatment refractory" (page 10, para 0032). However, relevant prior and post art literature does not disclose any methods or working examples for modulating sensorimotor gating in a subject having any neuropsychatric disease, such as bipolar disorder, causing a reduced PPI by administering any NT agonist, to the subject. The specification also does not disclose a method of improving cognitive function and memory attention, by administration of a pharmaceutically effective dose of any NT agonist, thereby treating a subject having bipolar disorder.

22. Due to the large quantity of experimentation necessary to modulate sensorimotor gating in a subject having any neuropsychiatric disorder by administering any NT agonist and thereby improving cognitive function and memory; lack of direction/guidance presented in the specification regarding the same; the complex nature of the invention; the absence of an appropriate animal model for bipolar disorder; the state of the prior and post art which has yet to determine clear nexus between all states of bipolar disorder,NT and PPI and, the unpredictability of treatment of neuropsychiatric diseases; undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

Claim Rejections - 35 USC § 102

23. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

24. Claims 15-18, 24-26 and 31 are rejected under 35 U.S.C. 102(b) as clearly anticipated by Feifel et al., (J Pharmacol & Expt Therap 288: 710-713, 1999).

25. Claims 15-18, 24-26 and 31 are directed to a method for modulating sensorimotor gating in a subject having inherently reduced pre-pulse inhibition (PPI), or any neuropsychiatric disorder causing a reduced PPI, by administering a neurotensin (NT) agonist, such as PD149163, to increase PPI (claims 15-18). The claims further recite the inhibition of serotonin receptor mediated neural function, or improving cognitive and memory attention, by administration of a NT agonist/pharmaceutically effective dose of any NT agonist, in a subject (claims 24-26, 31).

26. Feifel et al., teach that subcutaneous injections of NT agonist PD149163 (0.08-1 mg/kg) to male rats, resulted in a significant dose-dependent reversal of the PPI reduction produced by an indirect dopamine agonist, amphetamine (page

1999, Materials and Methods, Figure 1). Because the method steps disclosed by Feifel et al., meet the limitations of claims 15-18, 24-26 and 31 of the instant application, the method described in the reference anticipates the invention.

Conclusion

27. No claims are allowed.

28. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

Berrettini et al. Br J Psychiatry. 150: 208-212, 1987
(Reference showing the NT in the CSF of bipolar patients)

29. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aditi Dutt whose telephone number is (571) 272-9037. The examiner can normally be reached on Monday through Friday, 9:00 a.m. to 5:00 p.m.

30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

31. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information

for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov/. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AD
19 December 2006

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER